Meeting Report
Centers for Medical Countermeasures against Radiation (CMCR) Program
November 7th and 8th, 2005
Crystal City Sheraton
Arlington, VA

Division of Allergy, Immunology and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)

CMCR Awardees

To expand the medical options available to triage, prevent and/or treat radiation-induced injury, and thereby help minimize terrorist threat, the NIAID, NIH established eight Centers for Medical Countermeasures against Radiation (CMCRs) in September 2005. These Centers include Columbia University, Dana Farber Cancer Institute, Duke University, Fred Hutchinson Cancer Research Center, Medical College of Wisconsin, University of California, Los Angeles, University of Pittsburgh, and the University of Rochester Medical Center.

Purpose of the Meeting

The primary objective of this initial meeting was to promote synergistic interactions among the centers, facilitate interactions between centers, government and commercial laboratories and coordinate research activities for the overall program.

About the Meeting Attendees

In addition to CMCR Principal Investigators (PIs) and their staff, attendees included PIs from institutions funded by Project Bioshield: Protecting the Immune System against Radiation (awarded by NIAID in July 2005); as well as contractors receiving funding for product development support for radiation countermeasures (Medical Countermeasures against Radiological Threats, Product Development Support Services, awarded by NIAID in September, 2005), and Development of an Improved Diethylenetriaminepentaacetate (DTPA) for Improved Radionuclide Chelation (awarded by NIAID in September, 2005).

Also, scientists from the United States national research laboratories (Argonne, Lawrence Livermore, Los Alamos, Oak Ridge, and Sandia) participated in the meeting. A number of military and government agency representatives were also in attendance, including the National Cancer Institute, Armed Forces Radiobiology Research Institute, Centers for Disease Control, Defense Advanced Research Projects Agency, Defense Threat Reduction Agency, Department of Energy, Department of Homeland Security, Food and Drug Administration, Homeland Security Council, Office for Public Health Emergency Preparedness, and the Office of Science and Technology Policy.

Background about the CMCR program

With increased activity of global terrorist organizations and a rise in illicit trafficking of radioactive materials, the threat of nuclear or radiological attacks has grown. For this reason, the CMCR program was designed to address the need for novel radiation countermeasures, as well as technologies/devices to rapidly determine radiation dose received. The CMCRs have been organized to serve as multidisciplinary centers comprised of academic, commercial, and government laboratories. The Centers are funded to: 1) move candidate countermeasures through the regulatory process into the national stockpile; 2) develop techniques and devices to provide accurate dose assessment in a triage scenario; 3) conduct basic and translational research to identify new countermeasures; 4) develop and validate new animal models or *in vitro* assays to evaluate countermeasures or underlying biology; and 5) provide new or expanded education resources to improve expertise in radiobiology. Synergistic interaction with other Centers and the NIH is a key feature. Each Center

provides unique and complementary strengths in terms of technical potential and specific areas of investigation, and all Centers share responsibility for program development, resource sharing and collaborations with other CMCRs. Each Center has four components: (1) at least three RO1-like projects; (2) core facilities to support projects or facilitate management; (3) short-term pilot projects; and (4) an education/training program.

Meeting Summary – Day One

The first morning consisted of presentations from United States government representatives, who provided CMCR scientists with a general context for their research work. These presentations included talks on governmental contingency and emergency response planning as well as government acquisition of stockpileable agents. Presentations on the science behind radiation events were also provided, and NIAID staff outlined their expectations for the CMCR program.

The meeting began with a welcome from Dr. Narayani Ramakrishnan, the program officer for NIAID's CMCR program. She discussed the goals of the program, which include development of tools and techniques for biodosimetry, and development of prophylactic, mitigating and therapeutic agents for radiation injury. She emphasized that the purpose of the meeting was to coordinate research activities within the CMCR network and facilitate interactions between the centers and outside interests.

Dr. Anthony Fauci, Director of the NIAID, then discussed how the CMCRs fit into the overall NIAID Biodefense program. He outlined NIAID's involvement in biodefense research for CDC Category A-C agents, including the priorities for therapeutics, vaccines, diagnostics, basic research and expansion of research capacity. Much like the CMCRs, the NIAID Regional Centers of Excellence (RCE) consist of multidisciplinary research groups, and include training programs and basic and translational research. Dr. Fauci outlined some key advancements made by the RCEs in vaccine development, and concluded his presentation by discussing the goals and design of the CMCR program.

The next speaker, Dr. Jerome Donlon, Chief Scientist, spoke about the goals of the DHHS Office of Public Health Emergency Preparedness (OPHEP). The mission of OPHEP is to "prepare for, protect against, respond to, and recover from all acts of bioterrorism and other public health emergencies that affect the civilian population". Dr. Donlon discussed the organization of the office, and the role of its different offices in coordinating Project Bioshield procurement and DHHS countermeasure research and development activities (Office of Research and Development Coordination); development and integration of policies for catastrophe contingency care (Office of Mass Casualty Planning); leading the DHHS response as well as training and directing emergency response teams (Office of Emergency Operations and Security Programs); and oversight of medical policies for countermeasure use (Office of Medicine, Science and Public Health).

Dr. Rajeev Venkayya, Director of Biodefense and Health from the White House Homeland Security Council discussed the ongoing government planning to deal with possible weapons of mass destruction events. He presented the structural hierarchy for the government response to natural (e.g. hurricanes, pandemic flu) or deliberate attack (radiological, chemical or biological). He stressed that for the government to respond to catastrophic events all agencies need to work together, not only in the planning, but also in the response phases. Across government, all agencies are expected to fully exploit their capabilities in order to protect the United States. Dr. Venkayya finished his talk by discussing the healthcare perspective, speaking of the challenges to medical personnel dealing with a radiation or other event, including availability of beds, doctors and nurses to care for exposed individuals. He also touched on the need to have delivery and distribution mechanisms in addition to new countermeasures; however, he pointed out that without new therapies, all other issues are irrelevant.

Also from OPHEP, Dr. Monique Mansoura, Senior Planning Officer, spoke about the Project Bioshield radiation countermeasures procurement program. She discussed the medical countermeasures pipeline and the acquisition process, and also outlined the three key aspects of the Bioshield procurement program: 1)

accelerated research and development, 2) acquisition (secure funding for countermeasure purchase) and 3) availability (emergency use authorization). Recent accomplishments of the program include anthrax vaccine products as well as contracts for pediatric potassium iodide (KI). Taking into account Material Threat Assessments (MTAs), DHHS estimates casualties from an attack scenario and uses this information to evaluate probable countermeasure efficacy. Dr. Mansoura concluded her talk by discussing the conditions, terms and challenges for Project Bioshield acquisitions, and outlined recent Bioshield implementations.

The next speaker, Dr. C. Norman Coleman, Director of the National Cancer Institute's Radiation Oncology Sciences Program, updated the conference participants on efforts to develop radiation/nuclear contingency plans. Dr. Coleman began by discussing some basic radiation science, including human LD_{50} estimations, and the acute radiation syndrome that follows exposure to certain radiation doses. He discussed concept of operations and challenges in the planning process, including drug development, product selection, intervention and people tracking. The Radiological Event Management System was also explained, as a means of providing concise, reliable and rapid information in the case of an attack. Expert groups are currently meeting in order to ensure that the information contained within this computer database is accurate.

Dr. Frederick Harper, a Senior Scientist from Sandia National Laboratory provided information about the characteristics of radiological dispersal devices (RDD) and how they affect the selection of medical countermeasures. Dr. Harper began with background about the types of radiation and pathways of release. He next discussed how particle size is extremely important in the dispersion of radioactivity, and how the type (e.g. α, β, or γ-emitter) and the form of the radiation (e.g. salt, ceramic or metal) can dramatically impact possible health effects resulting from exposure. He presented information about the "availability" of different types of radiation sources to terrorists, and detailed the kinds of RDD aerosolization studies that have been carried out at Sandia to accurately model dispersions that might occur following a radiological event or attack. These studies have taken into account a number of variables, including weather, cityscape and type of release.

Dr. Daniel Rotrosen, Director of DAIT, NIAID, wrapped up the morning session by discussing NIAID's expectations for the CMCR program. He detailed prior federal efforts in the area of radiation countermeasure development and the goals of the current government program. He next outlined the strengths of the CMCR program including flexibility to address urgent research needs, and ability to progress from scientific discovery through product development. The integration of the CMCR program, within the framework of other federal efforts, as well as interactions of the Centers with NIAID-awarded contracts for product development was also discussed. After outlining the responsibilities of the CMCR steering committee, Dr. Rotrosen concluded his presentation by reiterating the goals of the CMCR meeting, including the selection of a steering committee chairperson, exchange of scientific information, and identification of potential collaborations and common CMCR requirements.

The agenda for the afternoon of day one and morning of day two was planned to allow the CMCR awardees to discuss the research programs that they plan to undertake. Dr. Paul Okunieff, PI from the University of Rochester Medical Center, gave the first presentation titled "Center for Biophysical Assessment and Risk Management following Irradiation". This Center plans to look at potential biodosimetry markers, and study the use of known or novel agents to mitigate radiation damage. The biodosimetry projects consist of the use of electron spin resonance signatures found in radiation-exposed teeth to determine dose received, assessing exposure by measuring DNA damage in skin cells, and identification of dose by high-throughput analysis of micronucleated reticulocytes. Other projects will study the role of inflammatory molecules in radiation damage and the efficacy of a large number of mitigating agents that alter inflammation and model pulmonary responses to internal and external radiation exposures. Overall, the Center will focus on low dose or low dose rate, chronic, and inhalation radiation exposures.

The Columbia University Center for High-Throughput, Minimally-Invasive, Radiation Biodosimetry, led by Dr. David Brenner was the next to present. Dr. Brenner explained that his Center is focused on biodosimetric

device design, with four biomarker approaches: 1) micronuclei, 2) γ-H2AX, 3) gene-profiling, and 4) metabolomic profiling. He explained the need for different biodosimetric endpoints for different situations. They plan to develop ultra-high throughput assays based on analysis of radiation-induced micronuclei formation and γ-H2AX foci in lymphocytes, exfoliated urine cells and buccal swabs. Another project will develop a fully-integrated biochip based on gene-expression signatures. This project includes design and production of microfluidics modules, as well as identification of gene-expression signatures. The goal is to produce a low-cost module for stockpiling. Dr. Brenner also spoke about their goal of developing a metabolomics-based portable dosimeter. Early data suggest that it may be possible to estimate dose based on time-dependent changes in metabolic signatures (e.g. prostaglandins). He concluded by discussing the Enterprise Content Manager System that will be used by researchers in the Center as an excellent program for data management.

The next group to present was from Fred Hutchinson Cancer Research Center. Dr. George Georges (PI), Dr. Amanda Paulovich and Dr. Marco Mielcarek of the Radiation Dose-Dependent Interventions Center discussed their development of protein- and mRNA-based assays to rapidly triage radiation victims, as well as development of cytokine and cell-based treatment protocols for treatment of radiation-induced hematopoietic injury. Projects dealing with biodosimetry include plans to develop a "dip-stick" for blood- or urine-based protein diagnostics, as well as a small hand-held chamber that can automatically perform RT/PCR for radiation-induced genes. The primary animal model for this Center will be the dog, whose radiation responses have been shown to correlate well with humans. Cytokine and cell-based treatment protocols include committed progenitor cell support in the presence or absence of cytokines, cord blood transplant, and HLA-haploidentical hematopoietic cell transplant.

Dr. Alan D'Andrea (PI) and Dr. Kalindi Parmar of the Dana Farber/Harvard Center for Medical Countermeasures against Radiation concluded the presentations for day one, by discussing how their Center has a different focus from the others. Their program focuses on the role of DNA repair enzymes in ameliorating radiation-induced genetic damage, with several projects dedicated to screening compounds that modify intracellular pathways known to be important in the radiation repair response, including Fanconi Anemia/BRCA. The researchers also plan to assess the efficacy of WW-85 (a ROS scavenger) in models of radiation damage, and plan to determine the possible role of cyclins and cyclin-dependent kinases in radiation-induced apoptosis. Their final project capitalizes on advancements in siRNA libraries to attempt to identify agents that prevent apoptosis and enhance maintenance and proliferation of stem cells.

Meeting Summary – Day Two

Day two began with a presentation by Dr. Nelson Chao about the Duke University Radiation Countermeasures Centers of Research Excellence (RadCCORE). This Center consists of several different areas of research including biodosimetry, repair of normal tissue injury, and immune reconstitution. The biodosimetry projects include the use of optical stimulation of luminescence to estimate radiation dose in teeth, as well as development of a tool based on radiation-altered gene expression profiles. In the area of normal tissue injury, the projects involve assessing the efficacy of somatostatin analogs for gastrointestinal (GI) injury, and superoxide dismutase (SOD) mimetics in lung injury, as well as use of human growth hormone for hematopoietic protection. The other projects include studies on: 1) activation of Wnt signaling in stem cells to stimulate proliferation, 2) assessing the efficacy of endothelial cells and conditioned medium to treat hematopoietic damage, 3) determining the role of several signaling molecules (MyD88, CIAS1, and CIITA) in radiation induced lung injury, and 4) looking at the role of enteric microbes in radiation-induced GI injury.

The next speakers were Dr. John Moulder (PI), Dr. Stephen Brown, Dr. Susan Doctrow and Dr. Richard Hill. This Center program is based at the Medical College of Wisconsin and is titled Post-Irradiation Interventions to Mitigate and Treat Non-Hematological Injuries. It will focus on mitigation and treatment of radiation injuries in the GI tract, central nervous system, kidneys and lungs. The Center plans to determine if angiotensin converting enzyme inhibitors, angiotensin II blockers, SOD/catalase mimetics, or other organ system-specific agents can effectively minimize radiation-induced damage.

The next speakers, Dr. William McBride (PI) and Dr. Robert Schiestl of the UCLA Center for Biological Radioprotectors discussed their three overlapping areas of research, involving primarily screening assays: DNA repair/radiation carcinogenesis, human radiosensitivity, and radiation response modifiers. Projects planned for the Center include identification of small molecules from libraries that, in a yeast assay, reduce hyper-recombination and DNA deletion frequency; use of a cell viability assay to screen compounds that increase lymphocyte survival following radiation; and assessment of the *in vitro* effects of candidate radiation countermeasures in normal human cells, and also in cells from patients with known or unknown radiation sensitivities. A mouse core facility will provide an extensive range of specialty mice necessary for the proposed work.

Dr. Joel Greenberger (PI), Dr. James Peterson and Dr. Valerian Kagan concluded the open session of the meeting with their University of Pittsburgh Center's presentation of Mitochondria Targeting against Radiation Damage. As the title implies, the research is focused on achieving radiation protection and mitigation by minimizing oxidative damage and stabilizing the mitochondria. Their research plans include: 1) optimization of SOD therapy using plasmid liposomes and development of an oral delivery system or skin patch; 2) understanding the mechanism of electron transport chain damage, and prevention of cardiolipin oxidation as a means of reducing radiation-induced apoptosis in cells of the lung, GI tract, oral mucosa and bone marrow; and 3) identification of small molecule targets for radiation protection, by determining mitochondrial sites for SOD production and oxidative damage.

The CMCR meeting concluded with a closed business meeting in the afternoon for the CMCR steering committee. This committee included the CMCR PIs as well as relevant NIH and DHHS staff. The purpose of this session was to discuss administrative and programmatic issues, including milestones, progress reports, future meetings and setting of policies.

Feedback from participants suggests that the meeting was very well received, and poster presentations, in place throughout the meeting, provided an entrée for discussions between CMCR staff and meeting attendees.